

General Policy Topics

Control of cholesterol: uncertainties yet to be resolved

Ischaemic heart disease is the foremost cause of death among both men and women in most Western countries. A high concentration of serum cholesterol, and specifically the fraction contained in low-density lipoproteins, is a potent risk factor for coronary atherosclerosis, and the persuasive evidence that interventions which lower plasma cholesterol concentrations also lower the risk of ischaemic heart disease (1) is set out elsewhere in this journal (see page 32).

For some years, all United States citizens over 20 have been urged to undergo screening for high serum cholesterol and to maintain their lipid profile within prescribed limits through dietary adjustment, if necessary supplemented with a lipid-lowering drug (2). In 1992, 26 million prescriptions for these drugs were dispensed in the United States alone (3). Elsewhere, they have been used less extensively because they have been largely reserved for patients with clinical evidence of coronary atherosclerosis who have not responded adequately to attempts at dietary control.

Those who favour deploying these drugs for primary prevention of heart disease point to the immense cost, particularly in Western societies, of treating angina pectoris and myocardial infarction (4) and to evidence that some 50% of all fatal heart attacks occur without warning in patients with no previous symptoms of ischaemia (5). In contrast, those who favour their use solely in secondary prevention question, firstly, the cost and feasibility of sustaining a substantial proportion of the adult population on lipid-lowering drugs (6). Secondly, they seek definitive assurance that the uncontested efficacy of these drugs is not offset by long-range adverse effects, including perhaps carcinogenicity (7).

Reservations regarding the safety of long-term lipid-lowering therapy extend back to the mid-1970s when the results were reported of a multicentre European trial of the lipid-lowering agent, clofibrate, in the primary prevention of ischaemic heart disease (8). The study involved 10 000 middle-aged

healthy male volunteers who had serum cholesterol concentrations in the upper-normal to high ranges and who were assigned at random to take either clofibrate or placebo for some five years. The serum cholesterol of those who received clofibrate fell by a mean of 9% over this period. This fall was associated with a decrease of some 25% in episodes of non-fatal cardiac infarction, although it had no demonstrable effect on the incidence of angina or fatal infarction. Offset against this benefit was an excess of deaths from non-cardiovascular causes (162 v 127), including cancer (72 v 54), among the treated patients. Although these differences were not significant in the formal statistical sense, they prompted many national regulatory authorities within Europe to limit the approved indications for cholesterol-lowering fibrates to the treatment of responsive, high-risk patients in whom other control measures, including diet, weight-reduction, exercise and good control of diabetes, had failed (9).

Subsequently, following a re-working of the results of this study (10), and on the basis of a comprehensive reassessment of 28 randomized trials involving the treatment of 50 000 subjects with a variety of lipid-lowering agents (11, 12), it has been argued that only 9 deaths (within a total of 687 non-cardiovascular deaths in treated subjects) are securely attributable to known adverse effects of specific drugs. Six of these 9 deaths resulted from complications of cholesterol gallstone disease among treated patients in the multicentre clofibrate study. This reassessment challenges the conclusions drawn in the published reports of three of the reviewed trials (13–15) — and four derivative meta-analyses (16–20) — in which dietary adjustment was associated with cancer (13), gemfibrozil with suicide (14), and colestyramine with violent death (15). None of these associations achieved significance in any single trial and it seems, for the most part, that the deaths in question were concentrated among men who either did not accept the treatment, or who had signs of chronic ill health on entry to the trial (11).

As yet, little information is available on which to judge the long-term safety of more recently introduced lipid-lowering agents, and of the statin group of compounds, in particular (3). The only

substantial information on the results of extended treatment derive from a comparison of simvastatin and placebo in some 4500 patients treated on average for about 5 years (21). Thus far, the follow-up results are reassuring: 68 reported deaths from cancer are evenly distributed between the two groups.

Meanwhile, earlier apprehensions refuse to fade away. Disconcerting results have been obtained in Finland at the end of a comparably large and extended trial of the fibrate-related compound, gemfibrozil (22, 23). At the same time, in the United States, confusion and disagreement have resurfaced over the findings and implications of carcinogenicity studies which have been submitted by manufacturers to support marketing applications for lipid-lowering drugs (4, 7, 24).

In the Finnish trial, total mortality — and mortality from cancer — is reported to be somewhat higher among patients who had taken gemfibrozil, as opposed to placebo, for 3.5 years within the primary prevention arm of the study (22). Although these differences have not at any stage attained statistical significance, there is no escaping the fact that the trend runs contrary to expectation. Particularly difficult to dismiss is an excess of deaths from coronary heart disease (12 vs 4) among patients who had taken gemfibrozil, but who had dropped out prematurely from the secondary prevention arm of this study (23).

The debate now engaged in the USA feeds on these concerns. Information provided by manufacturers in product labelling and published compendia is interpreted by one group to indicate that, whereas none of the fibric acid derivatives and statins have been shown to be mutagenic or genotoxic in routine drug development tests, they have all caused cancer in rodents, in most cases at exposures of "the same order of magnitude" as those generated clinically (24). This interpretation has been contested by others who understand, for instance, that the most widely used of these drugs — lovastatin and gemfibrozil — have been associated with cancer in experimental studies only above threshold doses that are, respectively, some 33-fold and 10-fold greater than clinically recommended doses (4).

If the publicly available summary data cannot be securely interpreted by professionals who have been involved for many years with lipid-lowering therapy, and if — as seems to be the case — they have no access to the full reports of the relevant

studies, uncertainty prevails. Calls for freer access to technical data held by regulatory authorities are made from time to time. They are resisted on the grounds that understanding is not advanced by placing in the public domain data that can be meaningfully interpreted only by professionals working in a related field. Manufacturers could, perhaps, best resolve the issue themselves by releasing to bona fide researchers, on a discretionary and conditional basis, information that is not commercially sensitive and that is required to support projects conducted in the public interest.

One factor which may have contributed to the current confusion is that, within the past few years, some regulatory authorities have followed calls to describe systemic dose-related toxicological findings in terms of the plasma concentrations at which they occur rather than in terms of the administered dose (25, 26). One of the protagonist groups (24) contends that lovastatin and gemfibrozil are identified in compendial entries as causing liver cancer in mice at blood levels, respectively, only 3 to 4 times and 10 times greater than those generated clinically (27). They contrast these findings with the requirements of a newly developed international guideline on carcinogenicity testing, which has been drawn up jointly by manufacturers and regulatory authorities (28). The guideline is based on the contention that some cancers invoked experimentally in rodents only at blood-levels some 25 times greater than those encountered in patients have been predictive of clinical risk (29).

It is disconcerting that these threads of information should surface now that millions of patients have long received these drugs. Non-genotoxic carcinogenicity, which is typically evident only above a definable dosage threshold, is generally assumed to be a consequence of drug-induced, dose-related derangements of physiological mechanisms. Long experience of conducting carcinogenicity tests in rodents has helped to refine their predictive value (30), but it has also underscored uncertainties inherent in all the available animal models (31). The way in which drugs are absorbed, distributed, metabolized or excreted frequently differs extensively between species; interspecies and interstrain differences in susceptibility to specific cancers are legion; drugs administered at dosages approaching the limit of tolerance may be metabolized anomalously, or they may have profound effects on cellular metabolism and division that do not occur at therapeutic dosage. The objective must be to design carcinogenicity tests having regard to all available

related toxicological data, to investigate any demonstration of non-genotoxic carcinogenicity by searching for underlying pharmacological and pathological correlates, and to assess and set out in formal terms the anticipated relevance of these findings to the proposed clinical use.

Amid the current uncertainty, fundamental realities have to be accepted. Carcinogenicity studies designed and executed up to 30 years ago will not necessarily comply with the standards operative today. Decisions on their implications, taken with due care and the best advice available at the time, may not match those that would be taken today. But the clock cannot be put back and the aim now should be to generate as efficiently as possible the data needed to define the benefits and risks of long-term lipid-lowering therapy on a drug-specific basis.

Above all, in this increasingly complex world, it is vital to promote epidemiological medicine as the scientific foundation of sound public health practice. New drugs, particularly those intended for long-term and widespread use, are inevitably released on the basis of reasonable expectation of safety and efficacy. It takes decades rather than years to generate definitive evidence regarding their impact on morbidity and mortality. During this time there will inevitably be dispute and dissent about the reliability and interpretation of data. Transparency is of the essence. If the situation were otherwise, there would be real cause for concern. Several of the articles contained in this issue of *WHO Drug Information* demonstrate the crucial need to develop collaboration and commitment between doctors, patients and funding agencies to ensure that the products of drug development are assessed, as well as used, to the best advantage of communities and individuals. There are setbacks and disappointments, but the underlying trend remains one of solid, and sometimes remarkable achievement.

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